REMARKS/ARUGMENTS

Upon entry of this amendment, claims 10, 11, 12, 15, 26-31, 35 and 36 will be canceled without prejudice or disclaimer of the subject matter recited therein, whereby claims 1-15, 24-31, 35 and 36 will be canceled. Claims 16-23 and 32-34 and 37 will remain pending. Claim 16 is the sole independent claim.

The amendment herein is properly entered after final rejection, because the amendment cancels independent claim 10 and claims depending directly or indirectly therefrom. Accordingly, this amendment seeks to reduce issues for consideration by the Examiner, and does not raise seek to introduce any new issue that would require further search and/or consideration by the Examiner. Therefore, entry of the present amendment is appropriate and respectfully requested.

Applicants stress that the cancellation of claims is without prejudice or disclaimer to the submission of subject matter included in the canceled claims in one or more continuation and/or divisional applications, and is made without expressing any agreement or acquiescence with the rejections of record.

Reconsideration and allowance of the application are respectfully requested.

Information Disclosure Statements

Applicants note that initialed copies of Forms PTO-1449 are attached to the vacated Office Action, but were not included with the Office Action mailed February 8, 2005 or the Final Office Action mailed November 15, 2005. Applicants requested that the

Examiner include initialed copies of the Forms PTO-1449 submitted on July 15, 2004 and January 12, 2004 in the response filed August 8, 2005, but the Final Office Action did not respond to this request nor did the Final Office Action include initialed copies of the forms.

Moreover, Applicants once again note that Kirpotin et al, Biochemistry 1997, 36(1), 66-75, is not initialed on the form filed July 15, 2004 that is attached to the vacated Office Action. Therefore, Applicants request that a completely initialed form be included with the next communication.

Applicants therefore once again request that completely initialed copies of the forms be included with the next communication from the Patent and Trademark Office. Therefore, the Examiner is requested to address this matter in the next communication from the Patent and Trademark Office.

Claim of Priority

Applicants **once again** note that this application claims priority of Japanese Application Nos. 11-115737, filed April 23, 1999, and 11-115738, filed April 23, 1999. In this regard, Applicants once again note that a copy of the Form PCT/IB/304 was submitted with the papers when entering the national stage. **The Examiner is therefore respectfully requested to acknowledge the claim of foreign priority in the next communication from the Patent and Trademark Office as well as receipt of the certified copies of the priority documents in this national stage application.**

Applicants have repeatedly requested confirmation of the acknowledgement of the claim of foreign priority and receipt of the certified copies in this national stage application. The Examiner is therefor requested to address this matter in the next communication from the Patent and Trademark Office.

Response To Rejections

The following rejections are set forth in the Office Action:

35 U.S.C. 102/103 Rejections

(a) Claims 10-34 are rejected under 35 U.S.C.102(b) as being anticipated by Tagawa, U.S. Patent No. 5,264,221 (Tagawa '221).

(b) Claims 10-12, 15-24 and 26-37 are rejected under 35 U.S.C.103(a) as being unpatentable over Tagawa '221.

(c) Claims 10-12, 15-24 and 26-37 are rejected under 35 U.S.C.103(a) as being unpatentable over Kirpotin et al. (Biochemistry, 1997) in combination with Tagawa '221.

(d) Claims 10-12, 26-31 and 35-36 are rejected under 35 U.S.C.103(a) as being unpatentable over Tagawa, U.S. Patent No. 5,556,948 (Tagawa '948), or Tagawa, U.S. Patent No. 5,686,101 (Tagawa '101).

(e) Claims 10-12, 15-24 and 26-37 are rejected under 35 U.S.C.103(a) as being unpatentable over Hosakawa, U.S. Patent No. 6,787,153 (Hosakawa '153), or Hosakawa, U.S. Patent No. 6,139,869 (Hosakawa '869).

Obviousness-type Double Patenting

(f) Claims 10-12, 15-23 and 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of Hosakawa '153.

(g) Claims 10-12, 15-23 and 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of Hosakawa '869.

In response to the rejections set forth in the Office Action, Applicants initially note that independent claim10 and the claims dependent directly or indirectly therefrom have been canceled. Therefore, rejection (d) is rendered moot, because it applies only to canceled claims. However, Applicants reserve the right to present arguments against this rejection in continuation/divisional applications.

With regard to the pending claims, Applicants note that independent claim 16 is directed to a liposome comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the

bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody. Thus, Applicants' independent claim 16 includes, amongst other features, that an amount of the bonded compound is 15 to 30 mole% and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome.

As previously noted by Applicants and as discussed with the Examiner during the above-noted interview, Applicants' specification, beginning at page 1, "Background Art" section, beginning in the second paragraph, discusses and contrasts Japanese Patent Unexamined Publication (Kokai) No. 4-346918 (hereinafter "JP '918") with the invention that is disclosed and claimed in the instant application. The Examiner is reminded that Tagawa '221 is a family member of JP '918, and this family relationship between Tagawa '221 and JP '918 is set forth in the Information Disclosure Statement, filed January 25, 2002. Despite the family relationship that has been presented on the record, the rejection neither indicates such relationship, nor does the rejection address any of the discussion of JP '918 in Applicants' specification.

Still further, it is once again noted that Tagawa '221 includes overlapping inventors with the present application, in that the inventors named in Tagawa '221 include, amongst other co-inventors, Toshiaki Tagawa and Saiko Hosokawa, who are the inventors of the presently claimed invention. Accordingly, Applicants have, by the present invention, has provided improvements over prior art of which they were

co-inventors. Similarly, Hosokawa '869 and Hosokawa '153 include, amongst other co-inventors, Toshiaki Tagawa and Saiko Hosokawa, and Tagawa '948 and Tagawa '101 include, amongst other co-inventors, Toshiaki Tagawa.

Applicants further remind the Examiner that Tagawa '221 specifically discloses that an amount of antibody of 5 mg per 100 mg of total lipids was used. In contrast, according to the present invention, an antibody is bound at 1.2 to 2 mg per 100 mg of total lipids, as defined in claim 16, which range is not taught or suggested by Tagawa '221. Further, by binding the recited amount of an antibody to the liposome according the present invention, unexpectedly high tumor-suppressing effects can be obtained as demonstrated by Example 4 and Fig. 3. In general, one of ordinary skill in the art would expect that binding of a higher amount of an antibody would be attributable to higher selectability to a target antigen. In contrast, according to the present invention, a smaller amount of bound antibody is unexpectedly attributable to a higher suppressing effect against tumor proliferation. Accordingly, one of ordinary skill in the art would not have expected the advantageous effect of the present invention on the basis of common knowledge and in view of the prior art.

With respect to the rejections utilizing Tagawa '221, the Examiner maintains in the Final Office Action that Tagawa '221 discloses at column 4, lines 58-61, that the thiol-modified antibody is employed in an amount of 0.1% mol to 20% mol per mol of maleimide groups (with this amount being indicated by the Examiner to comprise an amount of antibody of 0.3 to 60 mg per 100 mg of the total lipid). Therefore, Applicants'

independent claim 16 and the claims dependent therefrom recite a range which is within a broader range disclosed by Tagawa '221, and the only specific disclosure of Tagawa '221 of the amount of antibody is in an amount of 5 mg of Fb' antibody for 100 mg of lipids, which is outside Applicants' recited range. Moreover, as noted above and as will be further discussed below, there is no motivation in Tagawa '221 to arrive at Applicants' claimed range, and Applicants have shown unexpected results. Therefore, Applicants' claims are not anticipated nor are they rendered obvious by Tagawa '221.

The Examiner states at page 3 of the Office Action that inhibitory effects are seen for a range of 0.5 to 5.3 mg/100 mg of total lipids. The Examiner contends that this statement clearly indicates that irrespective of whether the antibody amount is outside the claimed range or inside the claimed range the results are significant meaning that even in Tagawa '221 results are unexpected. However, the rejection does not address Applicants' arguments of unexpected advantages of not only using a smaller amount of bound antibody, but that when the amount of the bonded antibodies exceeded 2 mg/100 mg of the lipids, the retention in blood decreased depending upon the increasing amount of the bonded antibodies.

If the rejections of record are maintained, the Examiner is respectfully requested to specifically indicate where anticipation is present when the prior art of record does not specifically envisage Applicants' claimed subject matter. Moreover, the Examiner is respectfully requested to indicate how a prima facie case of obviousness is established

as well has how the obviousness rejection is appropriate in view of the unexpected showings established by Applicants.

Applicants therefore respectfully submit that the rejections of record should be withdrawn, and emphasize the above and other deficiencies in the rejections in the expanded arguments set forth below, whereby Applicants' claims are not anticipated, obvious or properly subjected to an obviousness-type double patenting rejection over the prior art of record.

Tagawa '221

Applicants once again note that Tagawa '221 discloses the use of a thiolated antibody in a ratio of 0.1 mol% to 20 mol% based on 1 mol of maleimide group (column 4, lines 9 to 7 from the bottom). Also, Tagawa '221 discloses in Example 3, a PEG modified liposome bound with an antibody. As explained in Example 3 of Tagawa '221, the liposome disclosed in Example 3 was prepared according to the method described in Example 2, which means that 100 mg of lipid was used for preparation of the liposome of Example 3. Moreover, in contrast to the liposomes recited in Applicants' claims, Tagawa '221 discloses in Example 2 (at column 7, lines 43-44) the preparation of a liposome by using 5 mg of Fb' antibody for 100 mg of lipids. Thus, Example 2 of Tagawa '221 discloses the use of 5 mg antibody per 100 mg of lipids.

The present invention as defined in Applicants' claims provides unexpected results, as will be discussed below, so as to achieve remarkable suppressive effect against tumor proliferation and superior retention in blood as compared with the

liposome with 5 mg antibody per 100 mg lipids. Applicants' originally filed specification, including Example 4, provides evidence of the unexpectedly advantageous results associated with Applicants' invention, In particular, in Example 4, liposomes 2-7 containing varying amounts of GAH antibody (0.5, 1.2, 2.0, 4.5, 5.3 and 11.4 mg) bonded to 100 mg of the total lipids of the liposome encapsulating doxorubicin (DXR, also referred to as adriamycin) were prepared according to the method of Example 1. Also, liposomes 1 bonded with no antibody were prepared. For the Examiner's convenience Table 3 from Applicants' specification including the content of the liposomes in the specification is once again reproduced below and modified to include conversion to amount of bound PEG (per 1 mol of maleimidated lipids). A discussion regarding the calculations regarding the conversion will once again be presented for the convenience of the Examiner following the discussion of Example 4.

Liposome disclosed in Example 4	Amount of bonded antibodies (mg/100 mg lipids)	Amount of included DXR (mg/100 mg lipids)	Amount of bonded PEG (mg/100 mg lipids)	Amount of bound PEG (per 1 mol of maleimidated lipids
1	0	9.5	8.2	28 mol%
2	0.5	9.1	8.2	28 mol%
3	1.2	9.5	8.1	28 mol%
4	2.0	8.9	5.3	18 mol%
5	4.5	9.6	6.2	21 mol%
6	5.3	9.7	6.4	22 mol%
7	11.4	10.0	3.2	11 mol%
Tagawa '221	Fab' antibody 5 mg			47 mol%

Example 4 further notes that retention of each liposome in blood was equivalent within the range of the amount of PEG bonded (> 4.4 mg/100 mg lipids), and Example 4 therefore indicates that the experimental results shown in the examples depended on the bonded amount of antibodies.

In Example 4, stomach cancer cell strain MKN45 was subcutaneously transplanted at two sites on nude mice. For the "efficacy test", administrations of liposomes with different amounts of bonded antibodies were started when the tumor reached to a size large enough to measure its long and short diameters. The dose of the liposomes was 5.0 mg/kg (as the amount of DXR) per administration, and a DXR-administered group (5.0 mg/kg) was provided as a positive control, and physiological saline was administered to the control group.

Significant inhibitory effects against tumor proliferation were found in all of the treated groups compared with the control group. A review of Fig. 3 in Applicants' application, when comparison is made to the DXR-administered group, reveals significant inhibitory effects against tumor proliferation in the samples with the amounts of bonded antibodies within the range of 0.5 to 5.3 mg/100 mg of total lipids. The inhibitory activity against tumor proliferation was observed with a peak in the vicinity of 2 mg/100 mg of total lipids as the amount of bonded antibodies.

In the "pharmacokinetic test", liposomes 4 to 7 with different amounts of bonded antibodies (2.0, 4.5, 5.3 and 11.4 mg/100 mg of total lipids) were intravenously administered to mice (each group consisted of 2 or 3 mice, 1.0 mg/kg as the amount of

DXR amount). Four hours after the administration, blood plasma was collected from each animal. The amount of DXR in plasma was measured by the fluorescence measurement method in the same manner as in Example 2. The amounts of DXR in plasma in the respective samples after the administration were compared to find correlation between the amount of bonded antibodies and the retention in blood of the liposomes encapsulating DXR and bonded with antibodies. In the pharmacokinetic test, correlation between the DXR amount in plasma after administration of each sample and the amount of bonded antibodies of each sample was obtained for samples having the amount of the bonded antibodies of 2 mg/100 mg of lipids or more, as can be seen from a review of Fig.4 in Applicants' application. As a result, it was found that, when the amount of the bonded antibodies exceeded 2 mg/100 mg of the lipids, the retention in blood decreased depending on the increasing amount of the bonded antibodies.

The conversion to amount of bound PEG (per 1 mol of maleimidate lipids) shown in the Table above can be calculated as follows. For example, liposome 1 shown in Table 3 is indicated to have the bonded PEG of 8.2 mg/100 mg lipids. The PEG used in Example 4 has the molecular weight of 10,000, which will be explained below, and therefore, the bonded PEG is 0.82 μ mol/100 mg lipids. The amount of maleimidated lipid per 100 mg lipids is 2.9 μ mol, which will also be explained below. Accordingly, the amount of bound PEG per 1 mole of maleimidated lipid is calculated as:

0.82 μ mol ÷ 2.9 μ mol x 100(%) = 28 mol%.

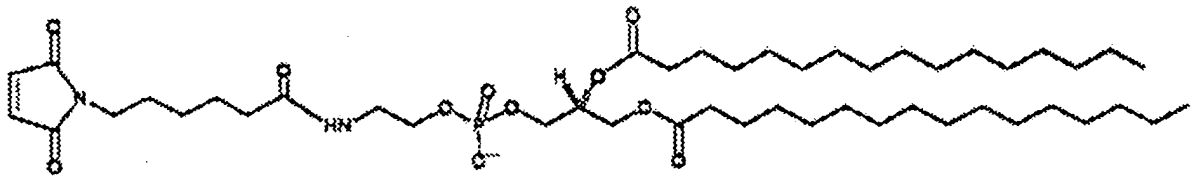
The amounts of the bound antibody and the bound PEG in the liposome disclosed in Tagawa '221 are 5 mg/100 mg lipids and 47 mol% per I mol of maleimidated lipids, respectively. It is further noted that the amount of the bound antibody and the bound PEG of the liposomes disclosed in Tagawa '221 are identical to those disclosed in Hosokawa '153 and Hosokawa '889.

Further, regarding the conversion and as noted above, the lIposomes disclosed in Example 4 were prepared according to the method of Example 1, as explained at page 17, line 2 in Applicants' specification. The liposome of Example 1 consisted of a mixture of dipalmitoylphosphatidylcholine (DPPC, M.W. 734, 18 moles), cholesterol (Cho, M.W. 346.7, 10 moles), and ε -maleimidocaproyldipalmitoylphosphatidylethanolamine (MC-DPPE, M.W. 884, 0.5 mol). The content of MC~DPPE in the total lipid can be calculated as follows:

DPPC :	Cho :	MCDPPE
18 mol	10 mol	0.5 mol
18 x 734	10 x 346.7	0.5 x 884
13212(A)	3467(B)	442(C)

A+B+C (g) : C (g) = 100 (mg) : Y(g)
Y(g) = 2.58mg → 2.58mg ÷ 442 = 2.9 μmol

Structure of MC-DPPE (M.W. 884)



With regard to the molecular weights of the PEGs, a two-chain type PEG which is referred to as "PEG 2000" and a two-chain type PEG which is referred to as "PEG 5000" were used in the Examples. Specifically, the explanation of "thiolated PEG (30 mg/mL, a two-chain type PEG having a molecular weight of 2000 (PEG 2000) and a two-chain type PEG having a molecular weight of 5000 (PEG 5000))" is given in Applicants' specification at page 12, lines 3 to 1 from the bottom.

Applicants remind the Examiner that they previously attached a specification for "PEG 5000" which was attached to a product purchased on behalf of Applicants, another copy of which is attached for the Examiner's convenience. In this specification, the product was named as "Sun-Bright SHPEG2" by a manufacturer, and as a result of quality test, the product was found to have a molecular weight of 11,000 which is within the standardized range of 10,900 to 13,000 specified by the manufacturer.

Accordingly, unexpected results are shown for the liposome recited in Applicants' independent claim 16 comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

The Examiner points to a broader range disclosed by Tagawa '221 and also contends that 4.5 is close to 5. However, the Examiner is once again reminded that in accordance with case law such disclosure should not be considered to be anticipation. In this regard, as stated in MPEP 2131.03, Rev.2, May 2004, II. PRIOR ART WHICH TEACHES A RANGE WITHIN, OVERLAPPING, OR TOUCHING THE CLAIMED RANGE ANTICIPATES IF THE PRIOR ART RANGE DISCLOSES THE CLAIMED RANGE WITH "SUFFICIENT SPECIFICITY", When the prior art discloses a range which touches, overlaps or is within the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." For example, if the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims.

In the instant situation, Applicants respectfully submit that there is not sufficient specificity so as to comprise anticipation and the claimed invention is not clearly envisaged in Tagawa '221. This lack of anticipation is also readily evident from the unexpected results. Also, it would not have been obvious to manipulate the amount of antibody or the amount of antibody and polyethylene glycol in Tagawa '221 to arrive at

Applicants' invention, especially in view of the unexpected results associated with Applicants' invention.

Still further, as stated in MPEP 2131.03, Rev.2, May 2004, III. PRIOR ART WHICH TEACHES A VALUE OR RANGE THAT IS VERY CLOSE TO, BUT DOES NOT OVERLAP OR TOUCH, THE CLAIMED RANGE DOES NOT ANTICIPATE THE CLAIMED RANGE, "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account." Accordingly, anticipation cannot be present when, in the instant situation, the values to do overlap or touch.

Thus, Applicants respectfully submit that Tagawa '221 does not teach each and every element as recited in Applicants' claims whereby the anticipation rejection is without appropriate basis. In particular, the obviousness rejection utilizing this same document is evidence of a lack of anticipation because the same claims are separately rejected under 35 U.S.C. 103(a) due to differences between Applicants' claimed invention and the disclosure of Tagawa '221. For example, Applicants once again note that the obviousness rejection specifically states that, "Tagawa's does not teach the entire claimed range of the bonded compound and the bonded antibody."

Expanding upon the above, Applicants emphasize that throughout their originally filed application patentable differences are set forth over the disclosure of Tagawa '221. In this regard, the Examiner's attention is once again directed to Applicants' specification

at page 2, first full paragraph wherein the subject matter of Tagawa '221 is contrasted with reference being made to the 5 mg addition of antibodies as noted above in Example 2 of Tagawa '221.

Moreover, beginning in the next paragraph on page 2 of Applicants' specification and continuing through page 3, the advantages of Applicants' invention are further discussed.

Also, as discussed above, the unexpected advantages of using a smaller amount of bound antibody according to Applicants' invention is also apparent from a review of Applicants' Example 4. As explained in Example 4, a smaller amount of bound antibody gives a higher therapeutic effect, and this result is unexpected by one of ordinary skill in the art in view of Tagawa which discloses the use of a larger amount of bound antibody than the presently claimed liposome, medicament composition and method.

As noted above, the claimed invention relates to liposome modified with the specified amount of the antibody as mentioned above and also modified with a specified amount of polyethylene glycol, i.e., 15 to 30 mole%. Tagawa '221 fails to teach or suggest the claimed range of polyethylene glycol in combination with the specified amount of antibody. The combination of the specific amount of antibody and the specific amount of polyethylene glycol of the liposome of claim 16 would not have been obvious to one of ordinary skill in the art, and the advantageous effects of the liposome would also not have been expected by one of ordinary skill in the art.

Kipotin does not overcome the deficiencies of Tagawa '221. In this regard, the rejection based upon Kirpotin relies upon Tagawa '221 in an attempt to arrive at Applicants' claims. However, for the reasons set forth above, there is not teaching or suggestion in Tagawa '221 to arrive at Applicants' claims.

Accordingly, the anticipation and obviousness rejections based upon Tagawa '221 should be withdrawn.

Hosokawa '153 and Hosokawa '869

As previously noted by Applicants, Hosokawa '153 and Hosokawa '869 disclose the antibody GAH. However, as discussed above, the antibody according to the presently claimed invention as defined in Applicants' independent claim 16 as comprising a bonded compound containing a polyalkylene glycol moiety bound to the liposome through thioether groups and a separately bonded antibody bound to the liposome through thioether groups, said liposome comprising lipids whose partial component has maleimidated terminal, and wherein an amount of the bonded compound is 15 to 30 mole% based on one mole of the maleimidated lipid, and an amount of the bonded antibody is 1.2 to 2 mg per 100 mg of total lipids that constitute the liposome, and said antibody comprising a GAH antibody.

As noted above, the presently claimed liposomes have unexpectedly high suppressive effect against tumor proliferation and superior retention in blood as compared with the liposome with 5 mg antibody per 100 mg lipids disclosed in Tagawa

'221. Hosokawa '153 and Hosokawa '869 also disclose the same amount of antibody and the same amount of PEG as Tagawa '221.

Accordingly Hosokawa '153 and Hosokawa '869 do not teach or suggest the subject matter recited by Applicants, and rejections based upon these documents should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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Form FA-16

試 験 成 績 書

サンプル名：サンブライト SH-PEG2

Distribution of molecular weight

Lot No.：SY-003　　日付 98/4/17

手順書 No.	試験項目	規格 (Standard)	結果 (Result)	記入者
PAM-15	性状	白色～微黄白色粉末	微黄色粉末	三沢
PAM-15	溶状(A_{400})	<0.01	0.035	三沢
PAM-15	確認試験(1)	適 220～224nm に極大吸収	適	三沢
PAM-15	確認試験(2)	適 標準品と一致	適	三沢
PAM-13	分子量分布	10,000～15,000	11,000	三沢
PAM-13	半値幅	8,000～15,000	9,400～12,600	三沢
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	三沢
PAM-07	低分子 SH 成分比 (mol%)	<1.0	0.4	三沢
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAM-08	EDTA 含有量(%)	0.5～1.5	0.81	三沢
PAM-09	水分含量(%)	<2.0	0.87	三沢
PAM-10	強熱残分(%)	<0.5	0.34	三沢
PAM-12	エンドトキシン (EU/mg)	<0.02	0.0004	三沢

確認者：伊藤智　　QC m.　　98/4/17
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